Influence of a Pressure Gradient Distal to Implanted Bare-Metal Stent on In-Stent Restenosis After Percutaneous Coronary Intervention

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Background—Fractional flow reserve predicts cardiac events after coronary stent implantation. The aim of the present study was to assess the 9-month angiographic in-stent restenosis rate in the setting of optimal stenting and a persisting gradient distal to the stent as assessed by a pressure wire pullback recording in the entire length of the artery.

Methods and Results—In 98 patients with angina pectoris, 1 de novo coronary lesion was treated with a bare-metal stent. After stent implantation, pressure wire measurements (P_d=mean hyperemic coronary pressure and P_a=mean aortic pressure) were performed in the target vessel: (1) P_d/P_a as distal to the artery as possible (fractional flow reserve per definition); (2) P_d/P_a just distal to the stent; (3) P_d/P_a just proximal to the stent; and (4) P_d/P_a at the ostium. Residual abnormal P_d/P_a was defined as a pressure drop between P_d/P_a measured at points 1 and 2. Fractional flow reserve distal to the artery after stenting was significantly lower (0.88±0.21 versus 0.97±0.05; $P<0.001$), and angiographic in-stent binary restenosis rate was significantly higher (44.0% versus 8.1%; $P<0.001$) in vessels with a residual abnormal P_d/P_a. Residual abnormal P_d/P_a (odds ratio, 4.39; 95% confidence interval, 1.10 to 18.16; $P=0.034$), reference vessel size (odds ratio, 0.17; 95% confidence interval, 0.04 to 0.69; $P=0.013$), and stent length (odds ratio, 1.11; 95% confidence interval, 1.03 to 1.21; $P=0.009$) were predictors of angiographic in-stent restenosis after 9 months.

Conclusions—A residual abnormal P_d/P_a distal to a bare-metal stent was an independent predictor of in-stent restenosis after implantation of a coronary bare-metal stent. **(*Circulation*. 2007;116:2802-2808.)**

Key Words: atherosclerosis ■ collateral circulation ■ myocardial fractional flow reserve ■ restenosis ■ stents

Until recently, restenosis was a major problem in percutaneous coronary intervention (PCI). The introduction of coronary stents reduced the rate of restenosis,[1–4] but in-stent restenosis still appears in a number of patients. Studies using intravascular ultrasound and pathological studies have shown that angiographic stenoses are associated with diffuse atherosclerosis in the distal part of the coronary tree, although this may not be identified by coronary arteriography.[5]

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Coronary pressure measurement with determination of fractional flow reserve (FFR)[6,7] has been proposed as a supplementary technique for optimizing PCI results.[8–10] In addition, FFR has been shown to have a predictive value after PCI.[11,12] FFR measured after stenting with the pressure wire located distal to the stent indicates the effects on maximal flow of the stented segment and of the remaining part of the artery. A complete analysis of the coronary artery after PCI can be achieved by a pressure wire pullback during sustained hyperemia induced by intravenous adenosine. A pullback pressure recording in an epicardial coronary artery reflects the conductance of the entire artery as well as of the individual segments. In diffusely diseased coronary arteries, a marked pressure drop may occur between an implanted stent and the distal part of the artery.

The aim of the present study was to assess the in-stent restenosis rate in the setting of optimal stent implantation and a persisting pressure gradient in the vessel distal to the stent as assessed by a pressure wire pullback recording in the stented coronary artery.

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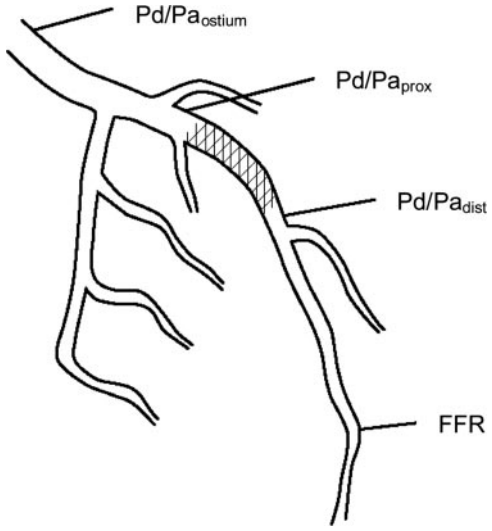

Figure 1. Illustration of different measurement points. FFR indicates FFR measured distal in the vessel; Pd/Pa$_{dist}$, P_d/P_a just distal to the stent; Pd/Pa$_{prox}$, P_d/P_a just proximal to the stent; and Pd/Pa$_{ostium}$, P_d/P_a at the ostium.

Methods

Patient Population

From October 2002 to December 2004, 98 patients with a single lesion in a native coronary artery and planned PCI were enrolled at Odense University Hospital, Aarhus University Hospital, Skejby Sygehus, or Rigshospitalet, Copenhagen, Denmark. Patients with a total occluded artery or acute myocardial infarction were excluded. All patients were on aspirin (75 mg/d) and clopidogrel (loading dose 300 mg 24 hours before PCI, continued on 75 mg/d for 12 months). A total of 88 patients (90%) had a 9-month angiographic follow-up. The study population was divided into 2 groups: group I, patients with a pressure gradient in the nonstented part of the vessel distal to the stent; and group II, patients without a pressure gradient distal to the stent. Stent names are shown in the online-only Data Supplement. The patients provided written, informed consent, and the local institutional review board (Scientific Ethics Committee for the counties of Vejle and Funen, Denmark) approved the protocol (case No. 20020045).

Intracoronary Pressure Measurements

Before pressure measurements and intervention, the patients had a 200-μg intracoronary nitroglycerin and a 5000- to 10 000-U intravenous heparin administration. A 0.014-inch pressure wire (PressureWire, Radi Medical Systems, Uppsala, Sweden, or WaweWire, JoMed, Helsinborg, Sweden) was passed through the target lesion and placed as distal to the coronary artery as possible. Maximal hyperemia was induced by intravenous adenosine (140 μg/kg per min), and the ratio P_d/P_a was calculated. Here, P_d represents mean hyperemic coronary pressure of the index vessel measured by the pressure wire, and P_a represents mean aortic pressure measured by the guiding catheter. After stenting, a slow manual pullback of the pressure sensor from the most distal position to the proximal part of the artery was performed at maximal hyperemia and recorded on paper. Pressure measurements were performed in the whole length of the artery: P_d/P_a was measured as (1) distal in the artery as possible (per definition of FFR), (2) just distal to the stent, (3) just proximal to the stent, and (4) and at the ostium (Figure 1). A residual abnormal P_d/P_a was defined as a pressure drop between hyperemic P_d/P_a measured at points 1 and 2. On the basis of the pressure measurements, 2 groups of patients were defined. In group I, hyperemic P_d/P_a point 1-hyperemic P_d/P_a point 2 was <0, and in group II, hyperemic P_d/P_a point 1=hyperemic P_d/P_a point 2.

Quantitative Coronary Angiography

Angiographic studies performed at baseline, after the procedure, and at follow-up were assessed at the Angiographic Core Laboratory (Catheterization Laboratory, Odense University Hospital, Odense, Denmark). The computer-based ACOM.PC V3.1 (Siemens Medical Systems, Inc) was used for quantitative coronary angiography. Quantitative analysis was performed offline by experienced personnel unaware of the pressure measurements. The same 2 projections were used at all time points. The following angiographic measurements were measured: reference diameter of the vessel, minimal luminal diameter, percent diameter stenosis [1−(minimal luminal diameter/reference segment diameter)×100], and late lumen loss (difference between minimal luminal diameter at the end of the procedure and at follow-up).

Study End Point and Definitions

The primary end point of the study was binary angiographic restenosis ≥50% after 9 months. Optimal stenting was based on visual estimates by the operator and defined as a residual stenosis of 0. The core laboratory qualitative comparative analysis could overrule the visual operator assessment.

Statistical Analysis

Statistical analysis was performed with the use of SPSS 14.0. Categorical data were presented as counts and percentages and compared by the Pearson χ^2 test or the Fisher exact test. Continuous data were expressed as mean±SD and compared by *t* test. Two-way ANOVA with 4 repeated measurements was used to test whether a significant change occurred in measurements at different wire positions. If this test was significant, a paired *t* test was used to compare the values between the relevant wire positions. Separate logistic regression analyses were performed to identify univariate predictors of binary angiographic restenosis, and a subsequent stepwise (forward conditional) regression analysis was performed with entry and removal criteria of 0.05 and 0.10, respectively. Logistic regression analyses were presented as odds ratio (OR) with 95% confidence intervals. All statistical tests were 2-tailed.

With anticipation of a mean binary angiographic restenosis (≥50%) rate of 25% after 9 months, the 166 patients enrolled provided 80% power and a 5% α level to detect a difference of 20% (event rate of 15% and 35%, respectively). A probability value <0.05 (2-sided) was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics and Procedural Results

The clinical features at baseline are shown in Table 1. Age and risk factors did not differ significantly between the 2 groups: group I with abnormal residual P_d/P_a (n=58) and group II without abnormal residual P_d/P_a (n=40).

Lesion Characteristics

The occurrence of 1- and 2-vessel coronary artery disease was similar in the 2 groups. Diameter stenosis and lesion type did not differ between the 2 groups. Lesions tended to be longer in patients with residual abnormal P_d/P_a (Table 2). Patients with residual abnormal P_d/P_a had more left anterior descending artery lesions and fewer left circumflex artery lesions treated. The reference diameter was significantly lower in patients with residual abnormal P_d/P_a compared with patients without residual abnormal P_d/P_a (2.9±0.6 versus 3.3±0.5; $P<0.001$).

Table 1. Baseline Characteristics

	Group I (Residual Abnormal P_d/P_a Ratio)	Group II (No Residual Abnormal P_d/P_a Ratio)	*P*
No. of patients	58	40	
Men, %	84.5	84.6	NS
Age, mean±SD, y	61.9±10.2	62.4±8.1	NS
Current smoker, %	27.6	20.5	NS
Hypertension, %	36.2	35.9	NS
Hypercholesterolemia, %	82.8	92.3	NS
Diabetes mellitus, %	8.5	19.0	NS
Body mass index, mean±SD, kg/m^2	26.3±4.0	27.9±4.0	NS
Prior myocardial infarction, %	43.1	35.9	NS
Prior PCI, %	6.9	7.7	NS
Stable angina pectoris, %	89.7	92.3	NS
1-vessel disease	67.8	69.0	NS
2-vessel disease	27.1	28.6	NS
3-vessel disease	5.1	2.4	NS
Medication			
Antianginal medication ≥2 drugs, %	21.1	33.3	NS
Aspirin, %	100	100	NS
Clopidogrel, %	100	100	NS
Statin, %	88.1	89.3	NS

NS indicates not significant.

FFR and P_d/P_a at Different Pressure Wire Positions

Preinterventional FFR was significantly lower in vessels with residual abnormal P_d/P_a compared with vessels without residual abnormal P_d/P_a (Table 2). FFR before intervention correlated inversely with the angiographic diameter stenosis ($r=-0.562$, $P<0.001$) (Figure 2). FFR increased significantly after PCI (0.95±0.09 versus 0.65±0.20; $P<0.001$). No artery showed a sudden increase in distal coronary pressure by pressure wire pullback. This indicated that the pressure gradient, observed in the distal part of the artery, was due to a continuous loss of pressure in the artery distal to the stented segment and was not caused by an angiographically undetected focal narrowing. After the intervention, a significant within-subject change of P_d/P_a occurred in the entire artery in patients with a residual abnormal P_d/P_a (group I) ($P<0.001$, 2-way ANOVA analysis; Figure 3), whereas the within-subject change of P_d/P_a did not differ significantly along the entire length of the artery in patients without a residual abnormal P_d/P_a (group II). In group I, FFR (pressure wire placed in the distal vessel) was significantly lower than hyperemic P_d/P_a just distal to the stent (0.88±0.12 versus 0.94±0.11; $P<0.001$). In both groups, a small trans-stent gradient was present (P_d/P_a just distal to the stent versus P_d/P_a just proximal to the stent) (group I, 0.94±0.10 versus 0.97±0.08, $P<0.001$; group II, 0.97±0.05 versus 0.99±0.04, $P=0.001$). In group I, 29.3% (n=17) of the lesions had no trans-stent pressure gradient, and in group II, 67.5% (n=27) of the lesions had no trans-stent pressure gradient ($P=0.001$).

Table 2. Lesion and Procedure Characteristics

	Group I (Residual Abnormal P_d/P_a Ratio)	Group II (No Residual Abnormal P_d/P_a Ratio)	*P*
No. of patients, %	58	40	
LAD/CX/RCA, %	30/40/30	57/10/33	0.004
Reference diameter, mm	2.86±0.56	3.27±0.53	0.001
Diameter stenosis, %	66.4±13.9	69.5±14.3	NS
Lesion type (A/B/C), %	21/68/11	33/59/8	NS
Lesion length, mm	14.8±8.6	12.2±4.9	0.072
Stent length, mm	18.2±8.9	16.0±6.5	NS
Direct stenting, %	40.0	35.1	NS
FFR before intervention	0.62±0.21	0.71±0.19	0.033
FFR after intervention	0.88±0.12	0.97±0.05	<0.001

Values are expressed as mean±SD unless otherwise indicated. LAD indicates left anterior descending artery; CX, circumflex artery; and RCA, right coronary artery.

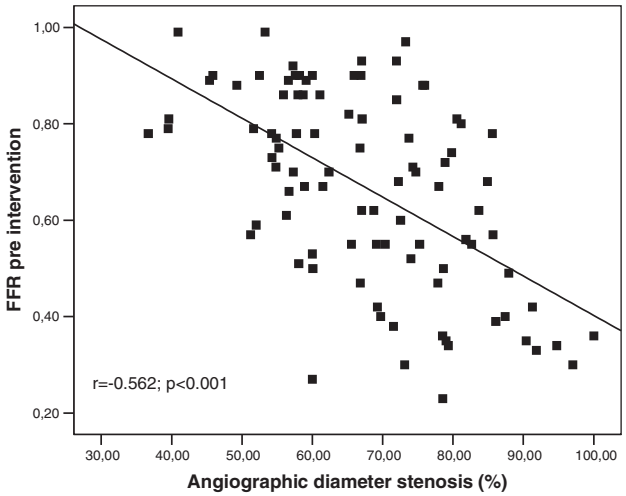

Figure 2. FFR vs angiographic diameter stenosis. FFR correlates inversely to the angiographic diameter stenosis.

FFR After PCI in the Individual Vessels With and Without a Residual Abnormal P_d/P_a Ratio Distal to the Stent

No significant differences in P_d/P_a were present just distal to the stent for the 3 major coronary arteries in group I (left anterior descending artery, 0.90±0.13; left circumflex artery, 0.98±0.08; right coronary artery, 0.94±0.07; P=NS) or group II (left anterior descending artery, 0.94±0.04; left circumflex artery, 0.98±0.06; right coronary artery, 0.97±0.04; P=NS). FFR after PCI was significantly lower in vessels with a residual abnormal P_d/P_a ratio compared with vessels without a residual abnormal P_d/P_a ratio (0.88±0.21 versus 0.97±0.05; P<0.001).

Angiographic Follow-Up and Event Rate

At 9-month follow-up, in-stent binary angiographic restenosis was demonstrated in 28.6% of patients with angiographic follow-up (Table 3) (25.7% of all patients). Target lesion revascularization was performed in 24.2% of patients with angiographic follow-up (21.8% of all patients). The in-stent binary angiographic restenosis rate was 21.1% (n=8) for right coronary artery lesions, 30.4% (n=7) for left anterior descending artery lesions, and 37.5% (n=9) for left circumflex artery lesions. In vessels with a residual abnormal P_d/P_a ratio, binary angiographic restenosis was seen in 44.0% compared with 8.1% in vessels without a residual abnormal P_d/P_a ratio (P<0.001). During the 9-month follow-up, no stent thrombosis was seen, and none of the patients died or suffered an acute myocardial infarction.

Predictors of In-Stent Binary Angiographic Restenosis

Logistic regression analysis was used to assess independent predictors of binary angiographic restenosis at 9 months. The parameters examined with the use of univariate logistic regression analysis are shown in Table 4. A residual abnormal P_d/P_a, reference vessel diameter, minimal luminal diameter after stent implantation, lesion length, and stent length were significantly associated with an increased rate of binary angiographic restenosis. To adjust for differences in lesion

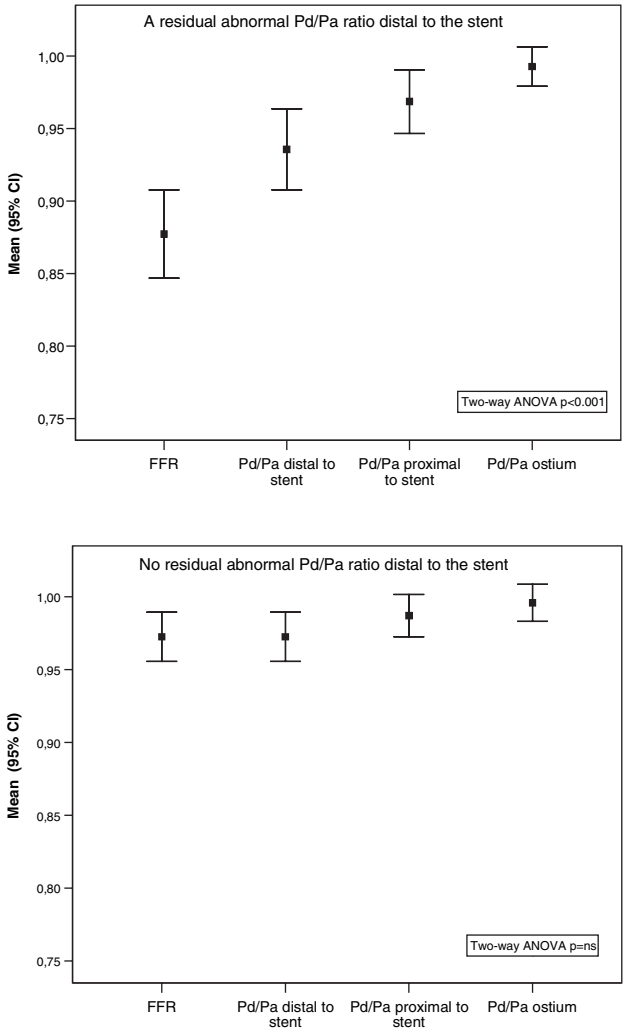

Figure 3. Mean values (and 95% confidence interval for the mean) of FFR distal in the vessel, hyperemic P_d/P_a just distal to the stent, hyperemic P_d/P_a just proximal to the stent, and hyperemic P_d/P_a at the ostium evaluated with a complete analysis of the stented coronary artery with a pullback pressure recording. Top, Patients with a residual abnormal P_d/P_a ratio (group I). Bottom, Patients without a residual abnormal P_d/P_a ratio (group II).

factors, we performed a multiple logistic regression analysis including the abnormal residual P_d/P_a ratio (as the variable of primary interest) and reference vessel diameter (as a well-known factor influencing binary angiographic restenosis) by forced entry and parameters with P<0.20 (from the univariate analysis) in a forward stepwise procedure. Included in the forward procedure were minimal luminal diameter after stent implantation, lesion length, stent length, FFR before PCI, and FFR after PCI. After these adjustments, a residual abnormal P_d/P_a ratio, reference vessel diameter, and stent length were found to be predictors of binary angiographic restenosis at 9 months (Table 5). Performing a backward stepwise procedure showed the same predictors of binary angiographic restenosis. The c statistic (area under the receiver operating characteristic curve) in the final model was 0.83.

Number of Patients Included

According to the power calculation, 166 patients were expected to be included. However, during the enrollment period

Table 3. Results of Quantitative Angiographic Analysis at Baseline and Follow-Up

	Group I (Residual Abnormal P_d/P_a Ratio)	Group II (No Residual Abnormal P_d/P_a Ratio)	*P*
No. of patients	58	40	...
No. of patients with angiographic follow-up	50	38	...
Before intervention			
Reference diameter, mm	2.86±0.56	3.27±0.53	0.001
Minimal lumen diameter, mm	0.41±0.06	0.47±0.08	NS
Diameter stenosis, %	66.4±13.9	69.5±14.1	NS
After PCI			
Reference diameter, mm	2.86±0.62	3.20±0.57	0.011
Minimal lumen diameter, mm	2.59±0.51	2.94±0.56	0.003
Diameter stenosis, %	8.1±11.0	7.6±11.8	NS
Follow-up			
No. of patients, n (%)	51 (84.7)	40 (90.5)	...
Reference diameter, mm	2.71±0.59	3.01±0.63	0.027
Minimal lumen diameter, mm	1.51±0.78	2.23±0.68	<0.001
Late lumen loss, mm	1.09±0.72	0.71±0.59	0.011
Diameter stenosis, %	45.3±25.0	25.9±17.0	<0.001
Binary angiographic restenosis, %	44.0	8.1	<0.001

Data are expressed as mean±SD unless otherwise indicated. NS indicates not significant.

the drug-eluting stents were implemented for clinical use, and the study was stopped before enrollment of the 166 patients in order not to have a selected cohort with bare-metal stents.

In regard to calculating the power with the observed difference of 44.0%−8.1%=35.9% in the event rate with binary angiographic restenosis, for a comparison of 2 independent binomial proportions with the use of the likelihood ratio statistic with a χ^2 approximation with a 2-sided significance level of 0.05, group sample sizes of 50 and 38 have an approximate power of 0.974 when the proportions are 0.44 and 0.081.

Table 4. Predictors for Binary Angiographic Restenosis (Univariate Analysis)

Variable	OR	95% CI	*P*
Age	1.03	0.97–1.09	NS
Diabetes mellitus	5.18	0.63–42.43	0.126
Smoking	1.33	0.46–3.84	NS
Study vessel*	0.83	0.26–2.70	NS
FFR before PCI	0.08	0.01–0.92	0.043
FFR after PCI	0.01	0.00–1.16	0.058
Residual abnormal P_d/P_a ratio distal to the stent	9.16	2.49–33.79	0.001
Lesion length	1.09	1.02–1.17	0.011
Reference vessel diameter	0.21	0.07–0.62	0.005
Minimum lumen diameter after stent implantation	0.24	0.08–0.70	0.009
Stent length	1.08	1.01–1.14	0.017
Angiographic diameter stenosis, %	1.01	0.97–1.04	NS

CI indicates confidence interval; NS, not significant.
*Circumflex as reference.

Discussion

The present study demonstrated that pressure reduction from an implanted stent to the distal part of the artery was a predictor of angiographic in-stent restenosis after 9 months. The pressure reduction was detected by a systematic analysis of the entire length of the stented coronary artery with a pullback pressure wire recording. A sudden increase in distal coronary pressure was not seen in any of the investigated arteries during the pullback procedure. Therefore, the pressure gradient observed in the distal part of the artery was due to a continuous loss of pressure in the artery distal to the stented segment and not to an angiographically undetected focal narrowing. A residual abnormal P_d/P_a ratio suggests diffuse disease in the remaining part of the artery, but diffuse disease was not documented by either angiography or intravascular ultrasound imaging.

In normal coronary arteries, no gradient exists between the ostium and the distal part of the artery despite induced hyperemia. In patients with angiographically mild disease, Gould et al[13] demonstrated a base-to-apex myocardial perfu-

Table 5. Predictors for Binary Angiographic Restenosis (Multivariable Analysis)

Variable	OR	95% CI	*P*
Residual abnormal P_d/P_a ratio distal to stent	4.58	1.11–18.84	0.034
Reference vessel diameter	0.17	0.04–0.71	0.014
Stent length	1.11	1.03–1.21	0.010

Predictors initially included in the model were as follows: residual abnormal P_d/P_a ratio distal to the stent, reference vessel diameter, minimum lumen diameter, lesion length, stent length, FFR before PCI, FFR after PCI distal to artery, and diabetes mellitus. CI indicates confidence interval.

sion gradient after dipyridamole administration by positron emission tomography without significant regional perfusion defects. It has been shown by coronary pressure measurements that a base-to-apex perfusion gradient can be due to abnormal resistance in atherosclerotic epicardial coronary arteries without segmental stenosis[5] because diffuse coronary atherosclerosis with no focal stenoses results in a graded, continuous pressure drop in the artery. This is in accordance with the findings of the present study, in which optimal coronary stenting resulted in a minimum hyperemic pressure drop within the stented coronary artery segment, whereas the transstenotic hyperemic gradient was not eliminated fully after stenting when the entire artery was evaluated. The minimum hyperemic pressure drop across the stented segment might indicate a small resistance to blood flow, but the present study was not designed to obtain a total elimination of the transstenotic hyperemic gradient after stenting.

After treatment with bare-metal stents, several studies have demonstrated that FFR predicts major cardiac events.[11,12] However, when FFR is reduced after stenting, it is important to distinguish between a persistent hyperemic gradient due to incomplete deployment and a gradient caused by diffuse disease proximal or distal to the treated lesion. Consequently, evaluation of stent deployment by FFR can be improved by calculations of P_d/P_a distal and proximal to the stent during maximal hyperemia to assess the conductance of the stented segment. In the present study, FFR distal to the artery tended to be related to development of in-stent restenosis.

Reference Vessel Size

The second independent predictor of angiographic in-stent restenosis after 9 months was reference vessel size. The ability to distinguish between large and small coronary arteries on the basis of quantitative coronary angiography is essential in PCI, and stent implantation in small arteries is a well-known independent risk factor of restenosis and major adverse cardiac events after PCI.[14–16] The mechanisms behind the unfavorable outcome for small vessels are not well understood. In addition to a small postprocedural lumen diameter, a high plaque burden and pronounced diffuse disease may be important factors.[17] Pathological and intravascular ultrasound studies have shown that an angiographically documented stenosis is associated with diffusely atherosclerotic changes in other parts of the coronary artery, although this may not be identified by coronary arteriography.[18–20] These findings are in accordance with the present study, in which coronary arteries without diffuse disease had a larger reference vessel diameter.

Pressure Pullback Recordings With Intravenous Adenosine

In the present study, maximum hyperemia was achieved with continuous intravenous adenosine infusion because intracoronary adenosine was too short-acting for a pullback recording. A pullback pressure recording in the epicardial coronary artery reflects the conductance of the entire artery as well as of every individual segment. A pullback recording during adenosine infusion has the potential to differentiate between diffusely diseased coronary arteries and a focal problem, such as a coronary lesion or an underexpanded stent.

Residual Abnormal P_d/P_a and Restenosis

Several mechanisms might influence our findings of increased binary restenosis rate in lesions with a residual abnormal P_d/P_a distal to the stent. Lesions with a residual abnormal P_d/P_a might not have been covered completely by the stent, and our intention to stent from disease-free to disease-free vessel might not have been achieved. In addition, a positive remodeling may have made a diffusely diseased artery look angiographically normal, and a diffusely diseased vessel might appear smaller because of lack of a normal reference segment. This might result in underexpansion or undersizing of the stent. The same degree of in-stent neointimal hyperplasia would contribute to a larger relative lumen reduction in a smaller stent size compared with a larger stent.

Study Limitations

Several limitations related to the study design should be taken into account. First, a low FFR and a low P_d/P_a without a focal step-up during a manual pullback through the artery is a pathophysiological finding that hypothetically can be applied to "diffuse disease," which is an anatomic description. However, we did not perform intravascular ultrasound imaging to confirm the presence of diffuse disease. Second, intravascular ultrasound imaging was not performed to confirm optimal stent expansion. Third, only disease distal to the stent was taken into account as a proximal and/or a distal "diffuse disease segment." Multiple segments within a patient should have been taken into account in the statistical analysis, and this could raise the question of whether either the distal or the proximal segment would be the strongest predictor, but the study was not powered for this determination. Fourth, the regression analyses for restenosis are based on 88 patients having 25 events only, as evidenced by the very wide confidence limits. In addition, we performed statistical tests with no accounting for multiple testing.

All patients were treated with bare-metal stents, and the overall angiographic restenosis rate was 25.7%, which is comparable to results with the placebo group in drug-eluting stent trials.[21,22] The use of drug-eluting stents has reduced restenosis rates dramatically, and our results cannot be extended to patients treated with drug-eluting stents.

Conclusion

A pullback recording during maximal hyperemia of a coronary artery treated with a stent is a rapid and simple method to analyze residual hyperemic gradients after coronary stenting. By this technique, it is possible to differentiate between a persistent gradient caused by incomplete stent deployment or by diffuse disease proximal or distal to the stent. Furthermore, a distal residual abnormal P_d/P_a seems to be a predictor of in-stent restenosis.

Disclosures

None.

References

1. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, Goy JJ, van den Heuvel P, Delcan J, Morel MA; Benestent Study Group. A comparison of balloon–expandable stent

implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med*. 1994;331:489–495.
2. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, Cleman M, Heuser R, Almond D, Teirstein PS, Fish RD, Colombo A, Brinker J, Moses J, Shaknovich A, Hirshfeld J, Bailey S, Ellis S, Rake R, Goldberg S; Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med*. 1994;331:496–501.
3. Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, Kiemeneij F, Ruygrok P, Ormiston J, Emanuelsson H, Fajadet J, Haude M, Klugmann S, Morel MA. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet*. 1998;352:673–681.
4. Jensen LO, Thayssen P, Kassis E, Rasmussen K, Saunamaki K, Thuesen L; Danish Percutaneous Transluminal Coronary Angioplasty Registry. Target vessel revascularization following percutaneous coronary intervention: a 10-year report from the Danish Percutaneous Transluminal Coronary Angioplasty Registry. *Scand Cardiovasc J*. 2005;39:30–35.
5. De Bruyne B, Hersbach F, Pijls NH, Bartunek J, Bech JW, Heyndrickx GR, Gould KL, Wijns W. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "normal" coronary angiography. *Circulation*. 2001;104:2401–2406.
6. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92:3183–3193.
7. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. *N Engl J Med*. 1996; 334:2401–2406.
8. Hanekamp CE, Koolen JJ, Pijls NH, Michels HR, Bonnier HJ. Comparison of quantitative coronary angiography, intravascular ultrasound, and coronary pressure measurement to assess optimum stent deployment. *Circulation*. 1999;99:1015–1021.
9. Fearon WF, Luna J, Samady H, Powers ER, Feldman T, Dib N, Tuzcu EM, Cleman MW, Chou TM, Cohen DJ, Ragosta M, Takagi A, Jeremias A, Fitzgerald PJ, Yeung AC, Kern MJ, Yock PG. Fractional flow reserve compared with intravascular ultrasound guidance for optimizing stent deployment. *Circulation*. 2001;104:1917–1922.
10. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation*. 2001;103:2928–2934.
11. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, Escaned J, Tsurumi Y, Akasaka T, Samady H, De Bruyne B; Fractional Flow Reserve (FFR) Post-Stent Registry Investigators. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. *Circulation*. 2002;105:2950–2954.
12. Klauss V, Erdin P, Rieber J, Leibig M, Stempfle HU, Konig A, Baylacher M, Theisen K, Haufe MC, Sroczynski G, Schiele T, Siebert U. Fractional flow reserve for the prediction of cardiac events after coronary stent implantation: results of a multivariate analysis. *Heart*. 2005;91:203–206.
13. Gould KL, Nakagawa Y, Nakagawa K, Sdringola S, Hess MJ, Haynie M, Parker N, Mullani N, Kirkeeide R. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base-to-apex myocardial perfusion abnormalities by noninvasive positron emission tomography. *Circulation*. 2000;101: 1931–1939.
14. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. *Circulation*. 1998;98:1875–1880.
15. Akiyama T, Moussa I, Reimers B, Ferraro M, Kobayashi Y, Blengino S, Di Francesco L, Finci L, Di Mario C, Colombo A. Angiographic and clinical outcome following coronary stenting of small vessels: a comparison with coronary stenting of large vessels. *J Am Coll Cardiol*. 1998;32:1610–1618.
16. Kasaoka S, Tobis JM, Akiyama T, Reimers B, Di Mario C, Wong ND, Colombo A. Angiographic and intravascular ultrasound predictors of in-stent restenosis. *J Am Coll Cardiol*. 1998;32:1630–1635.
17. Mintz GS, Popma JJ, Pichard AD, Kent KM, Salter LF, Chuang YC, Griffin J, Leon MB. Intravascular ultrasound predictors of restenosis after percutaneous transcatheter coronary revascularization. *J Am Coll Cardiol*. 1996;27:1678–1687.
18. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316:1371–1375.
19. Nissen SE, Gurley JC, Grines CL, Booth DC, McClure R, BerkM, Fischer C, DeMaria AN. Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. *Circulation*. 1991;84:1087–1099.
20. Mintz GS, Painter JA, Pichard AD, Kent KM, Satler LF, Popma JJ, Chuang YC, Bucher TA, Sokolowicz LE, Leon MB. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. *J Am Coll Cardiol*. 1995;25:1479–1485.
21. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R; RAVEL Study Group. Randomized study with the sirolimus-coated BX velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions: a randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773–1780.
22. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME; TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004;350:221–231.

CLINICAL PERSPECTIVE

Fractional flow reserve predicts cardiac events after coronary stent implantation. We assessed the 9-month angiographic in-stent restenosis rate in the setting of optimal stenting and a persisting gradient distal to the stent as assessed by a pressure wire pullback recording in the entire length of the artery. In 98 patients, 1 de novo coronary lesion was treated with a bare-metal stent. After stent implantation, pressure wire measurements (P_d=mean hyperemic coronary pressure and P_a=mean aortic pressure) were performed in the target vessel: (1) P_d/P_a as distal to the artery as possible and (2) P_d/P_a just distal to the stent. Residual abnormal P_d/P_a was defined as a pressure drop between P_d/P_a measured at the 2 points. Fractional flow reserve distal to the artery after stenting was significantly lower (0.88±0.21 versus 0.97±0.05; $P<0.001$), and angiographic in-stent binary restenosis rate was significantly higher (44.0% versus 8.1%; $P<0.001$) in vessels with a residual abnormal P_d/P_a. Residual abnormal P_d/P_a (odds ratio, 4.39; 95% confidence interval, 1.10 to 18.16; $P=0.034$), reference vessel size (odds ratio, 0.17; 95% confidence interval, 0.04 to 0.69; $P=0.013$), and stent length (odds ratio, 1.11; 95% confidence interval, 1.03 to 1.21; $P=0.009$) were predictors of angiographic in-stent restenosis after 9 months. The present study demonstrated that pressure drop from an implanted stent to the distal part of the artery was a predictor of angiographic in-stent restenosis after 9 months. A pullback recording during maximal hyperemia of a coronary artery treated with a stent is a rapid and simple method to analyze residual hyperemic gradients after coronary stenting.

Influence of a Pressure Gradient Distal to Implanted Bare-Metal Stent on In-Stent Restenosis After Percutaneous Coronary Intervention

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